Molina Clinical Policy
Skin Substitutes
Policy No. 357

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DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members.[1] References included were accurate at the time of policy approval and publication.

OVERVIEW

Normal healthy skin provides a protective barrier against microbes, water loss, and ultraviolet light damage; helps with thermoregulation; and provides tactile sensations. Wounds are disruptions of the skin's structural and functional integrity and normally transition through distinct phases until the skin's structure and function are restored. Wounds can be acute or chronic in nature. Usual care for chronic wounds involves removing necrotic tissue, applying dressings that maintain a moist wound environment, treating wound infections, and restoring blood flow to the wound site. If these procedures fail to restore the healing process, additional therapies such as the application of skin substitutes to promote wound healing may be considered (Snyder et al., 2020; Zenilman et al., 2013).

Skin substitutes are proposed as a treatment to cover open wounds and promote healing by preventing dehydration, reducing risk of infection, and providing a scaffold to support newly generated cells. The three most common uses for skin substitutes are for the treatment of venous leg ulcers, diabetic foot ulcers, and burns. Skin substitutes (also known as bioengineered, tissue-engineered, or artificial skin) are a heterogeneous group of products and can generally be classified into 3 main types: cellular (comprised of living cells), acellular (composed of synthetic materials or tissue from which living cells have been removed), or a combination of cellular and acellular components. Due to the unique characteristics of each skin substitute product, there is no simple, universally accepted classification system that allows for categorization of all the products that are commercially available. Selection of a skin substitute should take into account the type of wound, which layers of the skin are to be replaced, and the need for temporary vs. permanent placement (Shahrohki, 2021).

Skin substitutes are developed from different materials and therefore are evaluated by different Food and Drug Administration (FDA) pathways as outlined below ([1,2,3,4] FDA):

- Premarket Approval (PMA): devices that support or sustain human life or have the potential to cause risk of illness or injury are approved through the PMA process. This designation applies to skin substitutes that interact with body tissues after placement. Examples of products approved through the PMA process include Apligraf (P950032A) and Dermagraft (P000036A). For information on additional products, search by **product code MGR** (dressing, wound and burn, interactive) or applicant name in the PMA database.
- Premarket Clearance (510(k)): devices that are deemed substantively equivalent to legally marketed predicate devices and do not require a PMA can be marketed under this designation. Examples of products with 510(k) clearance include Oasis (K061711) and INTEGRA Wound Matrix (K210128). For information on additional products, search by **product code KGN** or applicant name in the 510(k) Premarket Notification Database.
- Public Health Service (PHS) Act 361 and 21 Code of Federal Regulations (CFR) 1270 & 1271]: Donated skin that is not substantially changed or processed is considered a banked human tissue. Human cells, tissues, and cellular and tissue-based products (HCT/Ps) are regulated by the Center for Biologics Evaluation and Research. Under CFR 1270 & 1271, HCT/Ps can only be commercially prepared by licensed establishments. Examples include TheraSkin and LifeNet Health. Establishments are required to screen and test donors, maintain records, and follow certain precautions to prevent the spread of communicable disease. Firms

must register and list their HCT/Ps with the FDA. Licensed establishments can be identified by searching the Human Cell and Tissue Establishment Registration database.

- Humanitarian Device Exemption (HDE): devices intended to treat diseases or conditions that affect fewer than 8,000 individuals in the United States per year may apply for a Humanitarian Device Exemption. There is currently one skin substitute, EpiCel (H9990002), approved for an HDE.

This MCP was developed according to various databases; in addition, there is an exhaustive list of skin substitute products. Some products are regulated by the FDA and sold in the United States through the PMA process, the 510(k) premarket clearance process, or the HDE process; or are regulated as human cells, tissues, and cellular and tissue-based products (HCT/Ps) derived from human cadaver skin and human placental membranes. Any list of commercially available skin substitutes should not be considered comprehensive due to the expanding nature of the industry and ongoing FDA approvals, including skin substitute products currently in development or in the clinical trial phase.

COVERAGE POLICY

NOTE: This policy does not address cellular products or breast reconstruction as Federal/State mandates apply.

Use of a skin substitute is considered medically necessary when **ALL** of the following indications are met:

1. The skin substitute product satisfies at least **ONE** of the following:

   a. The skin substitute product must meet all applicable regulations and standards established by the American Association of Tissue Banks for procuring and processing human cells, tissues, and cellular or tissue-based products (HCT/Ps); **OR**

   b. The skin substitute product must meet all product-specific FDA requirements that include **ONE** of the following:
      - The product has received FDA premarket approval for the requested indication; **OR**
      - The product has received FDA 510K premarket clearance for the requested indication; **OR**
      - The product has received FDA Humanitarian Device Exemption.

AND

2. The skin substitute product must be used for one of the following product-specific indications:

   a. **Allopatch.** Acellular human dermis derived from human allograft skin used for the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are present for at least 6 weeks with no exposure of capsule, tendon, or bone. Used in conjunction with standard diabetic ulcer care.
   b. **AmnioBand Membrane or Guardian.** Allograft made of human amnion and chorion used for the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than 6 weeks in duration with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care.
   c. **Apligraf (e.g., Graftskin).** Culture-derived human skin equivalent (HSE) used to treat:
      - Noninfected, partial and full-thickness skin ulcers due to venous insufficiency that are present for at least 6 weeks; **OR**
      - Full-thickness neuropathic diabetic foot ulcers nonresponsive to standard wound therapy diabetic foot ulcers and venous stasis leg ulcers; **OR**
      - Chronic, non-infected, partial and full-thickness venous stasis ulcer after a failure of at least 4 weeks of using regular dressing changes and therapeutic compression.
   d. **Artiss.** Slow-setting fibrin sealant consisting of human fibrinogen and low concentration human thrombin used for burns.
   e. **Biobrane.** Biosynthetic dressing used for a temporary covering of partial-thickness, freshly debrided or excised burn wounds in the absence of coagulum, eschar and necrotic tissue.
   f. **DermaCELL, Dermacell AWM, Dermacell Porous.** Acellular human dermis allograft collagen scaffold used for treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than 6 weeks in

duration with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care.

g. **Dermagraft.** Human fibroblast-derived dermal substitute used to treat lower extremity full-thickness diabetic foot ulcers on the fore foot, toes or heal, of longer than 6 weeks' duration, that extend through the dermis, and are refractory to standard wound care management.
h. **Epicel.** Cultured epidermal autograft used for deep dermal or full thickness burns comprising a total body surface area of greater than or equal to 30%. It may be used in conjunction with split-thickness autografts or alone in patients for whom split-thickness autografts may not be an option.
i. **Grafix Cellular Repair Matrix (Grafix Core, Grafix PL Core, Grafix Prime and Grafix PL Prime).** Cryopreserved, human placental, extracellular matrix treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than 6 weeks in duration with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care.
j. **Graftjacket Regenerative Tissue Matrix.** Acellular human dermal collagen template used for treatment of full-thickness diabetic foot ulcers greater than 6-weeks duration that extend through the dermis, but without tendon, muscle, joint capsule or bone exposure.
k. **Integra Bilayer Matrix Wound Dressing.** Collagen-glycosaminoglycan copolymers used for the treatment of severe burns, and partial and full-thickness neuropathic diabetic foot ulcers and venous ulcers.
l. **Integra Dermal Regeneration Template.** Collagen-glycosaminoglycan copolymers used for the treatment of severe burns and partial and full-thickness neuropathic diabetic foot ulcers.
m. **Integra Matrix.** Collagen-glycosaminoglycan copolymers used for the treatment of severe burns.
n. **OASIS Burn Matrix.** Extracellular matrix created from the submucosal layer of porcine small intestine used for burns.
o. **OASIS Wound Matrix & OASIS Ultra Tri-Layer Matrix.** Naturally derived, extracellular matrix (ECM) created from the submucosal layer of porcine small intestine. Oasis is an established treatment option for partial or full-thickness diabetic foot ulcers of greater than four weeks duration. Oasis may also be used to treat venous stasis ulcers of one-month duration that do not respond to standard wound care. The Oasis Ultra Tri-Layer Matrix incorporates three layers of the same structural components as the single layer matrix and is used in the treatment of larger wounds.
p. **OrCel.** Bilayered cellular matrix used for healing donor site wounds in burns.
q. **Suprathel®.** Synthetic epithelial substitute used for the treatment of first- and second-degree burns.
r. **TheraSkin.** Human skin allograft with epidermis and dermis layers used to treat partial or full-thickness, diabetic foot ulcer of greater than four weeks duration for which standard wound therapy has failed and partial or full-thickness venous stasis ulcer of greater than four weeks duration for which standard wound therapy has failed.
s. **TransCyte.** Human fibroblast-derived temporary wound cover used for full-thickness and deep partial-thickness thermal burns. It is used as a temporary wound covering until autograft is possible.

AND

3. **ALL** of the following are met:

   a. Member is age ≥ 18 years; **AND**
   b. Documentation noting that the Member is a non-smoker, or has completed or is currently in smoking cessation therapy; **AND**
   c. Wound characteristics and treatment plan are documented including **ALL** of the following:
      - Partial- or full-thickness skin defect, clean and free of necrotic debris, exudate, or infection; **AND**
      - Tissue approximation would cause excessive tension or functional loss; **AND**
      - No involvement of tendon, muscle, joint capsule, or exposed bone or sinus tracts; **AND**
      - No wound infection

AND

4. Additional criteria must also be met by condition, including **ONE** of the following**:**

   a. **Diabetic Foot Ulcer (DFU)** at least 1 cm^2 in size **ALL** of the following are met:
      - Hgb A1c of ≤ 8** or documentation of improving control; **AND**

- Wound has increased in size or depth or has not changed in baseline size or depth and there is no indication that improvement is likely (e.g., granulation, epithelialization, progress towards closing) after at least four (4) weeks of standard wound care including debridement, standard dressings, compression, and off-loading.
- Wound is without evidence of osteomyelitis or nidus of infection; **AND**
- Adequate circulation in affected extremity by physical examination or imaging (e.g., palpable dorsalis pedis or posterior tibial artery pulse or an ankle brachial index [ABI] of ≥.7 – 1.2 without calcification or evidence signifying a lack of fully calcified vessels such as triphasic or biphasic Doppler arterial waveforms at the ankle of affected leg); **AND**
- Applied in conjunction with conservative therapy (e.g., moist wound environment with dressings or non-weight bearing or pressure reduction interventions).

** Documentation may be required as studies are limited in patients with diabetic foot ulcers and related wounds.

OR

b. **Venous Leg Ulcers (VLUs)** at least 1 cm^2 in size and **ALL** of the following are met:
   - Wound has increased in size or depth or has not changed in baseline size or depth and there is no indication that improvement is likely (e.g., granulation, epithelialization, progress towards closing) after at least four (4) weeks of standard wound care including debridement, standard dressings, compression, and off-loading.
   - Adequate circulation in affected extremity by physical examination or imaging (e.g., palpable dorsalis pedis or posterior tibial artery pulse or an ankle brachial index ≥ 0.70); **AND**
   - Application is in conjunction with conservative therapy (e.g., compression wraps).

OR

c. **Partial- or full-thickness thermal burn wounds** when **ALL** of the following criteria are met:
   - Sufficient full-thickness autograft is not available at the time of excision or is not feasible due to the physiological condition of the Member; **AND**
   - No evidence of burn wound infection; **AND**
   - Excision of the burn wound is complete (e.g., nonviable tissue is removed) and homeostasis is achieved.

EpiFix Criteria

EpiFix (MiMedx) is a multi-layer biologic dehydrated human amniotic membrane allograft used to treat partial- and full-thickness diabetic foot ulcers and venous statis ulcers. Multiple treatments are typically required.

EpiFix **is considered medically necessary** for the treatment of diabetic foot ulcers when **ALL** of the following are met:

1. For the treatment of a partial- or full-thickness diabetic foot ulcer when standard diabetic ulcer care (e.g., surgical debridement, complete off-loading, standard dressing changes) of at least four (4) weeks duration has failed with no exposed capsule, tendon or bone; **AND**
2. Member has a diagnosis of Type 1 or Type 2 diabetes mellitus with a hemoglobin A1c (HbA1C) less than 8%; **AND**
3. Treated foot has adequate blood supply as evidenced by the presence of a palpable pedal pulse, an ABI of ≥ .7 – 1.2 without calcification, or evidence signifying a lack of fully calcified vessels such as triphasic or biphasic Doppler arterial waveforms at the ankle of affected leg.

For diabetic foot ulcers, a limit of two (2) applications may be authorized initially. Further applications are authorized at a minimum of one (1) week intervals, up to a maximum of four (4) applications in 12 weeks. Documentation of wound healing must be present (e.g., epithelialization, reduction in size of ulcer).

EpiFix **is considered medically necessary** for the treatment of venous stasis ulcers when **ALL** of the following are met:

1. For the treatment of a partial- or full-thickness venous stasis ulcer when standard wound treatment of at least four (4) weeks duration has failed; **AND**
2. Wound has been present for at least one (1) month and compression therapy of at least 14 days has been unsuccessful; **AND**
3. Treated lower extremity has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ABI of ≥ 0.70.

For venous statis ulcers, a limit of one (1) initial application will be authorized. Further applications are authorized at a minimum of one (1) week intervals, up to a maximum of four (4) applications in 12 weeks. Documentation of wound healing must be present (e.g., epithelialization, reduction in size of ulcer).

EpiFix **is considered experimental and investigational** for all other indications not listed above including, but not limited to the following:

- EpiFix application more frequently than once a week or beyond 12 weeks.
- EpiFix, particulate or injectable form.

Continuation of Therapy

ALL of the following guidelines for treatment apply:

- Continued treatment of chronic wounds will last no more than 12 weeks; **AND**
- Skin substitute applications must comply with FDA guidelines for the specific product and shall not exceed 10 applications or treatments per 12-week period of care or for Epifix, the limit is four (4) applications or treatments per 12-week period; **AND**
- Only one skin substitute will be simultaneously in place per wound episode. Product change within the wound episode is allowed, not to exceed the 10-application limit per wound per 12-week period of care. (NOTE: This may include a combination of skin substitute products; additional applications / products must be authorized).

Contraindications

Contraindications for the use of skin substitutes include **ALL** of the following:

- Active Charcot arthropathy of the ulcer surface
- Continued tobacco smoking – documentation should indicate that the Member has completed or is currently in smoking cessation therapy.
- Evidence of active infection or vasculitis in ulcer(s) targeted for treatment
- Exudate consistent with heavy bacterial contamination, or eschar or necrotic tissue that would interfere with graft take and healing
- Hypersensitivity or allergy to any components of the skin substitute (e.g., allergy to avian, bovine, porcine, equine products)
- Inadequate control of underlying conditions or exacerbating factors (e.g., uncontrolled diabetes with Hgb A1c > 8%, or no documented improvement of glucose levels in the last four (4) weeks
- Skin grafting or replacement for partial thickness loss with the retention of epithelial appendages, as epithelium will repopulate the deficit from the appendages, contraindicating the benefit of over-grafting

Limitations

1. Skin substitutes are **not medically necessary** for **ANY** of the following:
   a. Any indications not noted in the clinical criteria section above; **AND**
   b. Decubitus ulcer treatment; **AND**
   c. Continued treatment when the ulcer fails to heal by ≥ 50% within the first 6 weeks of treatment; **AND**
   d. Treatment beyond 12 weeks is considered not medically necessary regardless of wound status; **AND**

e. Continued skin substitute use after treatment failure, which is defined as the repeat or alternative application course (of up to 12 weeks) of skin substitute grafts within one year of any given course of skin substitute treatment for a venous stasis ulcer or diabetic foot ulcer; **AND**
f. Retreatment of healed ulcers (those showing greater than 75% size reduction and smaller than 1 square cm).

2. All other skin substitute products used for wound healing not outlined in the clinical criteria section above **are considered experimental, investigational, and unproven** due to insufficient evidence in the peer reviewed medical literature. Products include but are not limited to **ALL** of the following:

Actigraft
AlloDerm
AlloSkin or AlloSkin RT
AltiPly
AmnioAMP-MP
Amnioarmor
AmnioCore
AmnioCyte Plus
AMNIOEXCEL (including AMNIOEXCEL Amniotic Allograft Membrane)
AmnioHeal Plus
AMNIOMATRIX
Amnio-Maxx or Amnio-Maxx
AMNIOREPAIR
AmnioText or AmnioText patch
Amnio Wound
Amniply
Apligraft
Artacent (including Artacent Flex and Artacent Wound)
Arthroflex
Biobrane (except for indication specified in this policy)
BioNextPATCH
carePATCH
Cellesta products (e.g., Cellesta Amniotic Membrane, Cellesta Flowable Amnion)
Clarix Regenerative Matrix
Cogenex Amniotic Membrane or Cogenex Flowable Amnion
Coll-e-Derm
CoreCyte
CoreText
Corplex or Corplex P
Cryo-Cord
Cymetra
CYGNUS (including CYGNUS MATRIX, CYGNUS MAX, and CYGNUS SOLO)
Cytal (including Cytal Wound Matrix, MatriStem Wound Matrix, and Multilayer Wound Matrix)
Dermacyte Anmniotic Membrane Allograft Dermacyte Amniotic Wound Care Liquid
Derma-Gide
Derm-Maxx
EpiCord (including EpiCord Dehydrated Human Umbilical Cord Allograft)
E-Z Derm
FlexHD or Allopatch
GammaGraft
Genesis Amniotic Membrane
hMatrix
Hyalomatrix
Integra Flowable Wound Matrix
Interfyl
Kerecis Omega3
Keroxx (including Keroxx Flowable Wound Matrix)
Marigen Omega3
Matrion
MatriStem (including MatriStem Burn Matrix, MatriStem Micromatrix, and MatriStem Wound Matrix)
Mediskin
Memoderm
MIRODERM Biologic Wound Matrix
NEOPATCH
NEOX Wound Allograft
Novachor
Novafix DL
NuDyn
OrCel (except for indication specified in this policy)
PalinGen (including PalinGen Membrane, PalinGen XPlus Membrane, PalinGen XPlus Hydromembrane, PalinGen Flow, PalinGen SportFlow, ProMatrX ACF)
Phoenix Wound Matrix
PriMatrix
Procenta
ProText
PuraPly (including PuraPly Antimicrobial Wound Matrix, PuraPly AM, PuraPly AM XT, PuraPly XT)
REGUaRD
Restorigin
Revita
SkinTE
Strattice
Stravix
SurFactor
surgiGRAFT
SurgiMend
Talymed
TissueMend
Transcyte (except for indication specified in this policy)
TruSkin
Unite Biomatrix
XCellerate
XWRAP/XWRAP ECM

** Any other skin substitute not specified in this policy as medically necessary (according to criteria section) are considered experimental, investigational and unproven.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny

reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

The evidence suggests that skin substitutes appear to heal more chronic foot ulcers than standard wound care alone and may prevent amputation in patients with diabetes. Using skin substitutes may result in a lower incidence of wound infection and does not appear to present unique or serious safety concerns. Evidence suggests that more patients with chronic venous leg ulcers that do not heal with standard care alone experience complete healing when a bilayer human skin equivalent or allograft is used in addition to standard care. The evidence suggests that bioengineered skin substitutes for deep dermal burns appears to improve the long-term functional and cosmetic outcomes and increase quality of life. Benefits for other conditions using skin substitutes for wound healing have not been clearly demonstrated in robust clinical studies published in the peer reviewed medical literature. Evidence directly comparing different skin substitute products or types is extremely limited and insufficient to inform whether any one product or product type is superior to other products. Safety data were generally very limited but do not suggest skin substitutes are associated with serious harms or greater safety risks than standard care alone.

Burns

Burns can be full or partial thickness and may cause significant disability depending on the depth and body surface area (BSA) affected. Autografts remain the best treatment for burns; however, skin substitutes are used as an adjunct or temporary replacement to autologous grafting on partial or full thickness freshly excised burns. Evidence for the use of skin substitutes for treating burns is limited; small study size, the fragility of burn victims, and the inability to control confounding factors contribute to the difficulty in study design and execution. In practice, some FDA-approved skin substitutes are in use based on anecdotal evidence only. Although there was poor reporting of methodology, evidence from the small trials evaluated in one systematic review suggested that skin substitutes (e.g., Biobrane, TransCyte, Dermagraft, allogenic cultured skin) were as safe and at least as efficacious as topical agents, dressings, or allografts for treating partial thickness burns. (Burns et al., 2007; Pham, et al., 2007).

Less pain, shorter wound healing time and shorter hospital stays were observed with skin substitutes when compared to silver sulphadiazine dressings in another review of lower quality studies (Wasiak et al., 2013). FDA-approved skin substitutes have varying levels of medical evidence based on the product and the condition being treated. FDA approved skin substitutes for the treatment of burns by the 501(k) process are based only on evidence consisting of small unblinded studies of poor quality. For full or partial thickness burns with greater than 30% BSA involvement, the FDA has set up a process to allow the use of skin substitutes for patients who have sustained extensive tissue loss which necessitates a life-saving intervention. This humanitarian device exemption allows a hospital-based internal review board to approve and oversee the treatment of patients who qualify under the exception. (FDA[1,2,3,4]).

Diabetic Foot Ulcers

The International Consensus on the Diabetic Foot defines a diabetic foot ulcer as a full thickness wound peripheral to the ankle that may include exposure of underlying structures and is a complication of diabetes. Diabetic foot ulcers are difficult to treat and have a high recurrence rate. Skin substitutes may be used as adjunctive treatment for full thickness, chronic diabetic foot ulcers which have failed to heal with conservative methods (e.g., dressings, off-loading, non-weight-bearing). Some skin substitutes may not be appropriate for wounds with exposed underlying structures, an active wound infection, or certain conditions (e.g., Charcot's arthropathy, allergy to xenograft source). (Newrick, 2000).

In one multicenter, randomized trial, Dermagraft treatment for diabetic foot ulcers of greater than six weeks duration showed a 30% rate of healing in comparison to 18% healing when standard dressings were used (Marston et al., 2003). In a meta-analysis reviewing the use of acellular regenerative tissue matrix treatment for diabetic foot ulcers, complete wound healing was seen in 43% of patients compared to 30% with continued conservative treatment. In the same study, Apligraft and Dermagraft showed a significant change in the wound; Hyalograft-3D will need more studies to prove efficacy (Teng et al., 2010). FDA-approved skin substitutes have varying levels of medical evidence based on the product and the condition being treated (Felder, et al., 2012).

Venous Leg Ulcers

Venous leg ulcers form secondary to venous obstruction or reflux and are generally located on the leg below the knee. The diagnosis is confirmed by imaging (e.g., duplex ultrasound, plethysmography, venography, venous pressure measurement) in addition to clinical presentation. Ankle brachial index (ABI) measurement is helpful to rule out arterial occlusive disease and can be indicative of sufficient oxygenated blood flow to the wound. Revascularization, if indicated, is performed prior to wound treatment (Gloviczki et al., 2011).

Skin substitutes are an adjunct to compression dressings to treat noninfected partial or full thickness skin ulcers due to venous insufficiency of greater than four weeks duration. Living cell-based skin substitute grafts have been shown to increase the success of complete wound healing when applied to venous ulcers (Felder et al., 2012). Bilayer tissue-engineered skin substitute grafts showed complete wound healing after six months in 63% of the venous leg ulcers treated compared to 49% healing using simple compression dressings in one large study (Jones et al., 2013). FDA-approved skin substitutes have varying levels of medical evidence based on the product and the condition being treated.

Compression Therapy (CT)

Compression therapy (CT) remains the foundation of the management of patients with chronic venous insufficiency (venous valvular reflux). A range of garments and devices are available for CT to provide static or dynamic mechanical compression to part of the body region. Static compression for the treatment of lower extremity chronic venous insufficiency includes compression hosiery and bandages. Dynamic (intermittent) CT is provided via intermittent pneumatic compression pumps and sleeves; this option may benefit those with the presence of lymphedema. Research among patients with venous ulceration, the benefits of long-term compression therapy (e.g., stockings or bandages) have been continually demonstrated in randomized trials. Healing rates of 97% are achievable in patients with venous ulcers who are compliant with treatment. Benefits were also observed among patients with edema, weeping, or skin changes without ulceration. Contraindications for CT include patients with: peripheral artery disease, superficial or deep vein thrombosis, heart failure, and/or acute cellulitis, infection, or necrotic tissue. While research has been conducted in small trials, systematic reviews and meta-analyses support the use of elastic, multilayered compression versus inelastic, single-layer bandages for initial venous ulceration treatment. (Armstrong & Meyr, 2021).

Evans and Kim (2020) note medical literature supports local wound care and CT for the treatment of venous ulcers.

Mosti et al. (2020) conducted a retrospective study that found no significant differences in ulcer healing treated by compression therapy for patients using compression therapy versus diabetic patients (DP) and non-diabetic patients (NDP). The same treatment method was utilized for the patient population which included inelastic bandages and sclerotherapy of superficial venous reflux. Results show that CT is a safe treatment option for DPs with recalcitrant ulcers, including those with moderate peripheral arterial occlusive disease (PAOD). Further, CT in the DP population did not result in unwanted effects, however a minimum (not significant) healing delay was observed versus NDPs.

Compression Types

While inelastic bandaging (e.g., Unna boot) is effective, research shows that the addition of CT can lead to increased ulcer healing versus inelastic CT alone. High compression is more effective versus low compression; multilayer bandages are more effective to achieve the desired level of compression. While multilayered elastic bandaging systems are more expensive per use, improved patient comfort may increase compliance. A disadvantage is the level of experience needed to for proper application. (Armstrong & Meyr, 2021).

Compression hosiery can reduce physician visits and issues associated with bathing or wearing shoes. Disadvantages include hosiery soilage where there is significant fluid exudation from weeping ulcers. Research has found compression hosiery is effective versus use of elastic bandaging – initial therapy with two-layer compression stockings versus four-layer compression bandages had similar rates of ulcer healing (median healing time was 99 days). One systematic review noted that recurrence was lower for high-compression hosiery versus medium-compression hosiery at three years; in another trial, no difference was found at five years. Patients reported a high level of intolerance of the hosiery. Some patients do not have the ability to pull on compression stockings. Alternatives include stockings with a zipper and leggings with Velcro fastening bands. (Armstrong & Meyr, 2021).

Recurrence

Low patient treatment compliance (60-70%) can cause recurrence of venous ulcers, especially if wound healing has been achieved. Compliance with paste compression bandages is low as they can be uncomfortable leading patients to remove them in advance of the recommended duration. Compression stocking compliance is also low based on patient complaints (e.g., itching, tightness, difficulty with application, pins and needles sensation, and rash). The authors also note that patient beliefs that CT is ineffective to prevent recurrence lead to nonadherence. This could be improved through patient education and a positive experience during treatment of venous insufficiency. Materials are now used to make compression stockings with flexible, soft materials; some stockings feature zippers and Velcro fasteners to make them easier to use, especially older patients, and may increase compliance. The authors note that compliance is higher among patients with a mean age of 60 years – 76% were fully compliance with compression stocking use (Armstrong & Meyr, 2021).

Complications

Armstrong and Meyr (2021) note that most complications associated with compression bandaging are preventable. For example, lower extremity ischemia can develop when bandages are applied too tight. Patients should be educated to remove bandages if any of the following occur: numbness, tingling, or discoloration of the toes occurs. Medical attention should be sought if the symptoms do not immediately resolve. Additional complications include skin necrosis, fungal infection and contact dermatitis.

National and Specialty Organizations

The **International Society for Burn Injury (ISBI)** (2016) published the *ISBI Practice Guidelines for Burn Care*. The aim was to provide guidance for Providers treating those with burns to improve care overall. The ISBI also defined the most effective and efficient methods of evaluation and management of burn injuries. Topics developed in the current ISBI practice guidelines include the following:

- Organization and delivery of burn care
- Initial assessment and stabilization
- Smoke inhalation injury (diagnosis and treatment)
- Burn shock resuscitation
- Escharotomy and fasciotomy in burn care
- Wound care
- Surgical management of the burn wound
- Nonsurgical management of burn scars
- Infection prevention and control
- Antibiotic stewardship
- Nutrition
- Rehabilitation: positioning and splinting of the burn patient
- Pruritus management
- Ethical issues
- Quality improvement

The **Wound Healing Society (WHS)** has published the following guidelines related to this topic:

- *Arterial Ulcers*
- *Diabetic Foot Ulcer Treatment Guidelines*
- *Pressure Ulcers*
- *Venous Ulcers*

The **American Podiatric Medical Association (APMA) and the Society for Vascular Medicine (SVM)** published *The Management of Diabetic Foot: A Clinical Practice Guideline by the Society for Vascular Surgery*. Several recommendations are included regarding prevention, examination for peripheral neuropathy and education for patients and their families. Additional recommendations are provided on glycemic control to reduce DFUs, infections and risk of amputation. The recommendations also cover off-loading DFUs, diagnosis of diabetic foot osteomyelitis (DFO) and wound care for DFUs. (Hingorani et al, 2016).

The **National Institute for Health and Care Excellence (NICE)** (2019) published the document *Diabetic Foot Problems: Prevention and Management*. Recommendations address care of those admitted to the hospital and care across all settings. Assessing the risk of developing diabetic foot problems is covered as well as an overview of diabetic foot issues including ulcers and infection. The 2019 update included new recommendations on antimicrobial prescribing for adults with a diabetic foot infection.

The **Agency for Healthcare Research and Quality (AHRQ)** published a 2020 Technology Assessment – the document describes skin substitute products commercially available in the United States used to treat chronic wounds, examine systems used to classify skin substitutes, identify and assess randomized controlled trials (RCTs), and suggest best practices for future studies (Snyder et al., 2020). The report states:

> 74 commercially available skin substitutes were identified and categorized based on the Davison-Kolter classification system. Sixty-eight (92%) were categorized as acellular dermal substitutes, mostly replacements from human amniotic membranes and animal tissue sources. Three systematic reviews and 17 RCTs examined use of 13 distinct skin substitutes, including acellular dermal substitutes, cellular dermal substitutes, and cellular epidermal and dermal substitutes in diabetic foot ulcers and venous leg ulcers. Twenty-seven experimental ongoing clinical trials examined an additional 12 skin substitutes with similar classifications. Studies rarely reported clinical outcomes such as amputation, wound recurrence at least 2 weeks after treatment ended, and patient-related outcomes such as return to function, pain, exudate, and odor. The lack of studies examining the efficacy of most skin substitute products and the need for better-designed and -reported studies providing more clinically relevant data in this field is this Technical Brief's clearest implication.

Key findings in the 2019 document outlined include (Snyder et al., 2020):

- 74 commercially available skin substitutes were identified to treat chronic wounds. The majority of these do not contain cells and are derived from human amniotic membrane (the inner layer of the placenta), animal tissue, or human cadaver skin.
- 17 randomized controlled trials and 3 systematic reviews were included; experimental ongoing clinical trials will have examined only 25 (34%) of these skin substitutes by early 2019.
- Available published studies rarely reported whether wounds recurred after initial healing. Studies rarely reported outcomes important to patients, such as return of function and pain relief.
- Future studies may be improved by using a 4-week run-in period before study enrollment and at least a 12-week study period. They should also report whether wounds recur during 6-month follow-up.

Key findings for the 2020 update include the following statement (Snyder et al., 2020):

> 76 commercially available skin substitutes and categorized them based on the Davison-Kotler classification system. Sixty-eight (89%) were categorized as acellular dermal substitutes, mostly replacements from human placental membranes and animal tissue sources. Three systematic reviews and 22 RCTs examined use of 16 distinct skin substitutes, including acellular dermal substitutes, cellular dermal substitutes, and cellular epidermal and dermal substitutes in diabetic foot ulcers, pressure ulcers, and venous leg ulcers. Twenty-one ongoing clinical trials (all RCTs) examined an additional nine skin substitutes with similar classifications. Studies rarely reported clinical outcomes, such as amputation, wound recurrence at least 2 weeks after treatment ended, or patient-related outcomes, such as return to function, pain, exudate, and odor. The lack of studies examining the efficacy of most skin substitute products and the need for better-designed and reported studies providing more clinically relevant data in this field are this Technical Brief's clearest implications.

Additional 2020 report highlights include (Snyder et al., 2020):

- Ongoing clinical trials found during examine approximately 25 (33%) of these skin substitutes.
- Available published studies rarely reported whether wounds recurred after initial healing. Studies rarely reported outcomes important to patients, such as return of function and pain relief.
- Future studies may be improved by using a 4-week run-in period before study enrollment and at least a 12-week study period. They should also report whether wounds recur during 6-month follow-up.

SUPPLEMENTAL INFORMATION

Definitions

Acellular Products. Dermal substitutes made from natural biological materials includes decellularized human cadaver dermis, human amniotic membranes, and animal tissue. These are the most common commercially available skin substitute products for the treatment or management of chronic wounds.

Cellular Products.

Autograft: A sample of the patient's own healthy skin is harvested and placed in the ulcer in split- or full-thickness from pinch or mesh grafts or patients' cells may be grown in a laboratory to form a thin film (cultured keratinocyte autograft, or cultured epidermal autograft), which can take 3 to 4 weeks; their downside is the potential for donor site morbidity.

Allografts: Skin or tissue is harvested from another human such as a cadaver or from cultured keratinocytes or cultured epidermal fibroblasts.

Xenograft: Skin or tissue is harvested from an animal with similar skin structure (usually pigs or cows).

Bioengineered Products. Skin substitutes that may be completely synthetic (e.g., polymer matrix) or may be composite products (biosynthetic and contain 2 or more components which may be biological or synthetic).

Human Cells, Tissues, or Cellular or Tissue-based Products (HCT/Ps). Products containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.

CODING & BILLING INFORMATION

CPT Codes

CPT	Description
15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15272	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15274	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15275	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15276	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15277	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15278	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

HCPCS Codes

HCPCS	Description
C9250	Human plasma fibrin sealant, vapor-heated, solvent-detergent (Artiss), 2ml
Q4100	Skin substitute, not otherwise specified [Use for Biobrane, Epicel, OrCel, Suprathel]
Q4101	Apligraf per square centimeter

Q4102	Oasis wound matrix, per sq cm
Q4103	Oasis burn matrix, per sq cm
Q4104	Integra bilayer matrix wound dressing (BMWD), per sq cm
Q4105	Integra dermal regeneration template (DRT) or Integra Omnigraft dermal regeneration matrix, per sq cm
Q4106	Dermagraft per square centimeter
Q4107	GRAFTJACKET, per sq cm
Q4108	Integra matrix, per square centimeter
Q4121	TheraSkin, per sq cm
Q4122	DermACELL, DermACELL AWM or DermACELL AWM Porous, per sq cm~~f~~
Q4124	OASIS ultra tri-layer wound matrix, per sq cm
Q4132	Grafix core and grafixpl core, per square centimeter
Q4133	Grafix PRIME, GrafixPL PRIME, Stravix and StravixPL, per sq cm
Q4151	AmnioBand or Guardian, per sq cm
Q4155	Neox Flo or Clarix Flo 1 mg
Q4168	AmnioBand, 1 mg
Q4182	Transcyte per square centimeter
Q4186	Epifix, per square centimeter
A2011	Supra SDRM, per sq cm
A2012	Suprathel, per sq cm
A2013	Innovamatrix FS, per sq cm
A4100	Skin substitute, fda cleared as a device, not otherwise specified
Q4224	Human Health Factor 10 Amniotic Patch (HHF10-P), per sq cm
Q4225	Amniobind, per sq cm
Q4256	MLG-Complete, per sq cm
Q4257	Relese, per sq cm
Q4258	Enverse, per sq cm

Non-Covered HCPCS Codes

NOTE: Codes listed below for skin substitute products are considered non-covered and experimental, investigational and unproven. New codes may be added as necessary and prior to the policy's annual review. This list may not be all inclusive.

Q4100	Skin substitute, not otherwise specified [use for others not specified]
Q4110	Primatrix, per square centimeter
Q4111	Gammagraft, per sq cm
Q4112	Cymetra, injectable, 1cc
Q4113	Graftjacket xpress, injectable, 1cc
Q4114	Integra flowable wound matrix, injectable, 1cc
Q4115	Alloskin, per sq cm
Q4116	Alloderm, per square centimeter
Q4117	Hyalomatrix, per sq cm
Q4118	Matristem micromatrix, 1mg
Q4123	AlloSkin RT, per sq cm
Q4125	Arthroflex, per square centimeter
Q4126	MemoDerm, DermaSpan, TranZgraft or InteguPly, per sq cm
Q4127	Talymed, per sq cm
Q4128	FlexHD, or AllopatchHD, per sq cm
Q4130	Strattice tm, per square centimeter
Q4134	Hmatrix, per sq cm
Q4135	Mediskin, per sq cm
Q4136	E-Z Derm, per sq cm
Q4137	Amnioexcel, amnioexcel plus or biodexcel, per square centimeter
Q4138	Biodfense dryflex, per square centimeter
Q4139	Amniomatrix or biodmatrix, injectable, 1 cc

Q4140	BioDFence, per square centimeter
Q4141	Alloskin AC, per square centimeter
Q4142	Xcm biologic tissue matrix, per square centimeter
Q4143	Repriza, per square centimeter
Q4145	Epifix, injectable, 1 mg
Q4146	Tensix, per square centimeter
Q4147	Architect, Architect PX, or Architect FX, extracellular matrix, per square centimeter
Q4148	Neox Cord 1K, Neox Cord RT, or Clarix Cord 1K, per square centimeter
Q4149	Excellagen, 0.1 cc
Q4150	Allowrap DS or dry, per square centimeter
Q4152	DermaPure, per sq cm
Q4153	Dermavest and Plurivest, per sq cm
Q4154	Biovance, per sq cm
Q4156	Neox 100 or Clarix 100, per sq cm
Q4157	Revitalon, per sq cm
Q4158	Kerecis Omega3, per sq cm
Q4159	Affinity, per sq cm
Q4160	Nushield, per square centimeter
Q4161	bio-ConneKt wound matrix, per sq cm
Q4162	Woundex flow, bioskin flow, 0.5cc
Q4163	Woundex, bioskin, per sq cm
Q4164	Helicoll, per square cm
Q4165	Keramatrix or Kerasorb, per sq cm
Q4166	Cytal, per square centimeter
Q4167	Truskin, per square centimeter
Q4169	Artacent wound, per sq cm
Q4170	Cygnus, per sq cm
Q4171	Interfyl, 1 mg
Q4173	Palingen or Palingen Xplus, per sq cm
Q4174	Palingen or promatrx, 0.36 mg per 0.25 cc
Q4175	Miroderm, per sq cm
Q4176	Neopatch or Therion, per square centimeter
Q4177	Floweramnioflo, 0.1 cc
Q4178	FlowerAmnioPatch, per sq cm
Q4179	Flowerderm, per square centimeter
Q4180	Revita, per square centimeter
Q4181	Amnio wound, per square centimeter
Q4183	Surgigraft, per sq cm
Q4184	Cellesta or Cellesta Duo, per sq cm
Q4185	Cellesta flowable amnion (25 mg per cc); per 0.5 cc
Q4187	Epicord, per square centimeter
Q4188	AmnioArmor, per sq cm
Q4189	Artacent ac, 1 mg
Q4190	Artacent AC, per sq cm
Q4191	Restorigin, per square centimeter
Q4192	Restorigin, 1 cc
Q4193	Coll-e-derm, per square centimeter
Q4194	Novachor, per square centimeter
Q4195	PuraPly, per square cm
Q4196	PuraPly AM, per square cm
Q4197	Puraply XT, per square cm
Q4198	Genesis amniotic membrane, per square centimeter
Q4200	SkinTE, per sq cm

Q4201	Matrion, per square centimeter
Q4202	Keroxx (2.5g/cc), 1cc
Q4203	Derma-Gide, per sq cm
Q4204	Xwrap, per square centimeter
Q4205	Membrane graft or membrane wrap, per square centimeter
Q4206	Fluid flow or fluid gf, 1 cc
Q4208	Novafix, per sq cm
Q4209	SurGraft, per sq cm
Q4210	Axolotl Graft or Axolotl DualGraft, per sq cm
Q4211	Amnion Bio or AxoBioMembrane, per sq cm
Q4212	Allogen, per cc
Q4213	Ascent, 0.5 mg
Q4214	Cellesta Cord, per sq cm
Q4215	Axolotl ambient or axolotl cryo, 0.1 mg
Q4216	Artacent Cord, per sq cm
Q4217	WoundFix, BioWound, WoundFix Plus, BioWound Plus, WoundFix Xplus or BioWound Xplus, per sq cm
Q4218	SurgiCORD, per sq cm
Q4219	SurgiGRAFT-DUAL, per sq cm
Q4220	BellaCell HD or Surederm, per sq cm
Q4221	Amniowrap2, per square centimeter
Q4222	ProgenaMatrix, per sq cm
Q4226	MyOwn Skin, includes harvesting and preparation procedures, per sq cm
Q4227	AmnioCoreTM, per sq cm
Q4229	Cogenex Amniotic Membrane, per sq cm
Q4230	Cogenex Flowable Amnion, per 0.5 cc
Q4231	Corplex P, per cc
Q4232	Corplex, per sq cm
Q4233	SurFactor or NuDyn, per 0.5 cc
Q4234	XCellerate, per sq cm
Q4235	AMNIOREPAIR or AltiPly, per sq cm
Q4236	carePATCH, per sq cm
Q4237	Cryo-Cord, per sq cm
Q4238	Derm-Maxx, per sq cm
Q4239	Amnio-Maxx or Amnio-Maxx Lite, per sq cm
Q4240	CoreCyte, for topical use only, per 0.5 cc
Q4241	PolyCyte, for topical use only, per 0.5 cc
Q4242	AmnioCyte Plus, per 0.5 cc
Q4244	Procenta, per 200 mg
Q4245	AmnioText, per cc
Q4246	CoreText or ProText, per cc
Q4247	Amniotext patch, per sq cm
Q4248	Dermacyte Amniotic Membrane Allograft, per sq cm
Q4249	AMNIPLY, for topical use only, per sq cm
Q4250	AmnioAmp-MP, per sq cm
Q4254	Novafix DL, per sq cm
Q4255	REGUaRD, for topical use only, per sq cm
Q4262	Dual Layer Impax Membrane, per sq cm
Q4263	SurGraft TL, per sq cm
Q4264	Cocoon Membrane, per sq cm
Q4265	Neostim TL, Per Square Centimeter
Q4266	Neostim Membrane, Per Square Centimeter
Q4267	Neostim DL, Per Square Centimeter

Q4268	Surgraft FT, Per Square Centimeter
Q4269	Surgraft XT, Per Square Centimeter
Q4270	Complete SL, Per Square Centimeter
Q4271	Complete FT, Per Square Centimeter
A2001	Innovamatrix AC Per Sq Cm
A2002	Mirragen Advanced Wound Matrix Per Sq Cm
A2004	Xcellistem Per Sq Cm
A2005	Microlyte Matrix Per Sq Cm
A2006	Novosorb Synpath Dermal Matrix Per Sq Cm
A2007	Restrata Per Sq Cm
A2008	Theragenesis Per Sq Cm
A2009	Symphony Per Sq Cm
A2010	Apis Per Sq Cm
A2019	Kerecis Omega3 Marigen Shield, Per Square Centimeter
A2020	Ac5 Advanced Wound System (Ac5)
A2021	Neomatrix, Per Square Centimeter

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APPROVAL HISTORY

04/13/2023	Policy reviewed. Criteria consolidated. Criteria specific to line of business removed. Coverage in case of acute burn updated. Coverage of EpiFix sheet form clarified. Coding updated. AMR Peer Review. Policy reviewed on April 4, 2023 by an Advanced Medical Reviews (AMR) practicing, board-certified physician in the area of Wound Care.
02/09/2022	Policy reviewed, included Actigraft as non-covered.
12/08/2021	Policy reviewed; no changes to criteria; added HCPCS code Q4155 and removed Q4131; added national / specialty items from ASPS, ISBI, WHS SVS/APMA/SVM and updated references.
02/08/2021	Policy reviewed, clinical criteria updated with additional and comprehensive wound specific recommendations for burns, diabetic foot ulcers and venous leg ulcers. Coding updated with all products available. Contraindications and limitations updated; guidelines and references sections revised, condensed, and updated. AMR Peer Review. Policy reviewed on January 13, 2021 by an Advanced Medical Reviews (AMR) practicing, board-certified physician in the area of Plastic Surgery.
04/23/2020	New policy. AMR Peer Review. Policy reviewed on January 3, 2020 by an Advanced Medical Reviews (AMR) practicing, board-certified physician in the area of Plastic Surgery

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